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Health and Environmental Effects Profile for N,N-Diphenylamine

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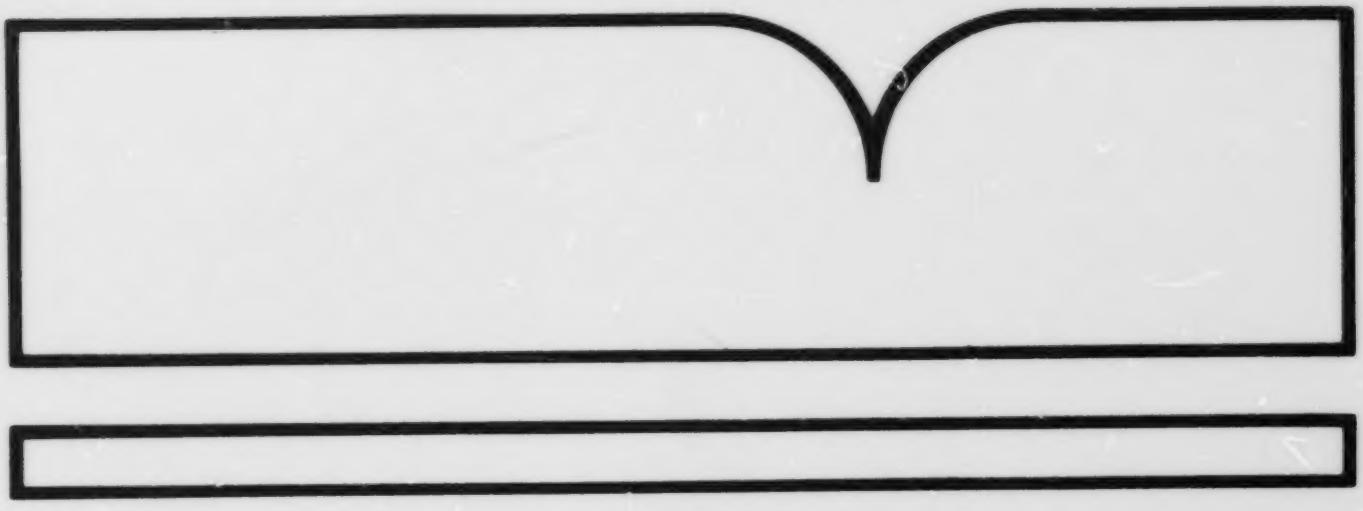

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR N,N-DIPHENYLAMINE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
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16. ABSTRACT

The Health and Environmental Effects Profile for N,N-diphenylamine was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. N,N-Diphenylamine has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for N,N-diphenylamine is 2.17 mg/day for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for N,N-diphenylamine is 1000.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1984.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

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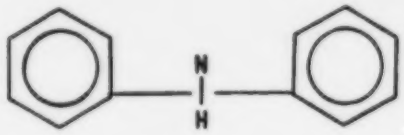
LIST OF ABBREVIATIONS

ADH	Alcohol dehydrogenase
ADI	Acceptable daily intake
AWT	Advanced waste water treatment
BCF	Bioconcentration factor
BSP	Bromosulfophthalein
bw	Body weight
CAS	Chemical Abstracts Service
CNS	Central nervous system
CS	Composite score
DNA	Deoxyribonucleic acid
GC/MS	Gas chromatography/mass spectrometry
K_{oc}	Soil sorption coefficient
K_{om}	Soil organic matter/water distribution coefficient
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
MED	Minimum effective dose
MTD	Maximum tolerated dose
NOAEL	No-observed-adverse-effect level
ppb	Parts per billion
ppm	Parts per million
ppt	Parts per trillion
RBC	Red blood cells
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

N,N-Diphenylamine or simply diphenylamine is also known by the synonyms DPA, N-phenylaniline, N-phenylbenzenamine and anilinobenzene. The structure, molecular weight and empirical formula for diphenylamine are as follows:



The molecular weight for diphenylamine is 169.23 and the empirical formula is $C_{12}H_{11}N$. The CAS Registry number for diphenylamine is 122-39-4.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Diphenylamine is a colorless to grayish crystalline solid at room temperatures (Verschueren, 1983) with a floral odor (Kouris and Northcott, 1963). It is soluble in alcohol, ether, benzene, carbon disulfide and most other organic solvents (Hawley, 1977; Kouris and Northcott, 1963). Selected physical properties of diphenylamine are listed below:

Melting point:	52.8°C (Verschueren, 1983)
Boiling point:	302°C (Verschueren, 1983)
Specific gravity:	
solid, 25°C	1.159 (Layer and Kehe, 1978)
liquid, 53°C	1.057 (Layer and Kehe, 1978)

Flash point:	153°C (Kouris and Northcott, 1963; Hawley, 1977)
Autoignition temperature:	1173°F (Hawley, 1977)
Water solubility:	
at 25°C	0.03 g/100g (Perry and Chilton, 1973)
at 25°C	300 ppm (Verschueren, 1983)
at 10°C	17.9 ppm (Layer and Kehe, 1978)
at 15°C	22.8 ppm (Layer and Kehe, 1978)
at 20°C	29.6 ppm (Layer and Kehe, 1978)
at 25°C	35.7 ppm (Layer and Kehe, 1978)
at 30°C	44.2 ppm (Layer and Kehe, 1978)
at 20°C	48-54 ppm (Hashimoto et al., 1982)
Vapor pressure, mm Hg:	
at 108.3°C	1 (Perry and Chilton, 1973)
at 141.7°C	5 (Perry and Chilton, 1973)
at 157.0°C	10 (Perry and Chilton, 1973)
at 222.8°C	100 (Perry and Chilton, 1973)
at 53°C	0.035 (extrapolated)
pK_a:	0.78 (Perrin, 1972) 0.80 (Rao and Hayon, 1975)
Log octanol/water partition coefficient:	3.50 (Hansch and Leo, 1981) 3.42 (Veith et al., 1979) 3.37 (Eadsforth and Moser, 1983)

Diphenylamine darkens on exposure to light (Kouris and Northcott, 1963), which is indicative of photolytic transformations. It is a weak base, and forms salts only with strong acids. It participates in a variety of chemical reactions, which is reflected in its commercial applications (Layer and Kehe, 1978).

1.3. PRODUCTION DATA

Production data for 1977 are listed in Table 1-1 (U.S. EPA, 1977). Current manufacturers listed by SRI (1984) are American Cyanamid in Bound Brook, NJ, ICI Americas (Rubicon Chemical) in Geismar, LA, and Morton

TABLE 1-1

Diphenylamine Production Data*

Producer	Type	1977 Production
Givaudan Corporation Clifton, NJ	manufacturer	none
Rubicon Chemical Geismar, LA	manufacturer	confidential
Nissho-Iwai America Corporation New York, NY	importer	1-10 million pounds
Intsel Corporation New York, NY	importer	10-100 thousand pounds
EM Labs Elmsford, NY	importer	confidential
Olin Corporation St. Marks, FL	importer	<1000 pounds
Ugine Kuhlmann Paramus, NJ	importer	confidential
Mobay Chemical Pittsburgh, PA	importer	confidential
American Cyanamid Bound Brook, NJ	importer	confidential
Mitsui and Company Cleveland, OH Houston, TX	importer importer	10-100 thousand pounds 0.1-1.0 million pounds
Conray Chemical Rockville Center, NY	importer	<1000 pounds
ICI Americas Wilmington, DE	importer	0.1-1.0 million pounds

*Source: U.S. EPA, 1977

Thiokol, Inc., in Moss Point, MS. USITC (1984a) lists Rubicon, Uniroyal and U.S. Steel Corporation as diphenylamine manufacturers in 1983. The most recent production figures reported for diphenylamine by the U.S. International Trade Commission are 34.7 and 39.9 million pounds in 1973 and 1974, respectively (USITC, 1974, 1976). Imports through major United States'ports of entry in recent years are as follows (USITC, 1982, 1983, 1984b):

Year	Imports (millions of pounds)
1983	0.61
1982	0.55
1981	0.10

Diphenylamine is manufactured by reacting aniline and HCl to form aniline hydrochloride, which is then heated with aniline to yield diphenylamine (Layer and Kehe, 1978). Excess aniline is removed from the reaction products by distillation for recycling, while the crude diphenylamine is purified via vacuum distillation.

1.4. USE DATA

Diphenylamine is used widely in the production of industrial antioxidants for polymers, greases and oils (Kuney, 1984; Layer and Kehe, 1978). Approximately 1-2% of some type of diarylamine is added to almost all commercial synthetic rubbers for oxidation protection (Layer and Kehe, 1978). Diphenylamine itself has only minor antioxidant uses in rubber, but its derivatives and other types of diarylamines have major uses.

Diphenylamine is used commercially as an intermediate in the synthesis of agricultural chemicals, dyes and pharmaceuticals (Kuney, 1984). It is added (200-300 ppm) as a polymerization stabilizer to vinyl acetate that is to be stored for indefinite periods (Daniels, 1983). As a stabilizer, diphenylamine is also used in cellulose nitrate explosives (Layer and Kehe,

1978). Diphenylamine is added (up to 1 wt%) to various gun propellant compositions (Lindner, 1980). Apples and pears can be dipped in diphenylamine solutions or wrapped in paper treated with diphenylamine to inhibit the development of scald disease during periods of prolonged cold storage (Layer and Kehe, 1978). Diphenylamine and its chloro derivative have shown insecticidal activity.

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

The fate of diphenylamine in water will depend on its ability to undergo chemical, photochemical and biological reactions and to partition from one environmental matrix into another. The UV spectrum of diphenylamine shows significant absorbance in the range of 290-310 nm (Sadtler, 1960) which indicates the potential for direct photolysis in the environment. Lopez et al. (1980) found that the direct photolysis (the wavelength of light used was unavailable in the abstract of this study) of dilute aqueous solutions of diphenylamine produced a carbazole product in water containing oxygen, and carbazole plus tetrahydrocarbazole in degassed water. Also, several investigators reported that the direct photolysis of diphenylamine in various organic solvents produces carbazole (Raju et al., 1974, 1975; Puri and Sidhu, 1972). In addition, the photolysis of diphenylamine in organic solvents at wavelengths >300 nm has been found to be photosensitized by a variety of organic compounds such as ketones, anthracene, naphthalene, methylene blue, rose bengale, eosin, benzophenone and dyes (Raju et al., 1974, 1975; Puri and Sidhu, 1971, 1972; Bansal et al., 1974, 1975a,b; Puri et al., 1973a,b; Santhanam et al., 1976). In addition to carbazole, the photosensitized photolysis of diphenylamine has produced a diphenylnitroxide product. Experimental data pertaining to the photolysis of diphenylamine in aqueous solution with such environmental photosensitizers as humic and fulvic acids were not located; however, these substances may increase photolysis rates in the aquatic environment. Unfortunately, aqueous photolysis rate data that could be extrapolated to environmental situations were not located in the available literature as cited in the Appendix; therefore, the significance of photolysis cannot be quantified.

The biodegradation of diphenylamine has been studied by several authors. Gardner et al. (1982) examined the microbial degradation of ring-labeled ^{14}C-diphenylamine in a laboratory model sewage sludge system. Activated sludge was obtained from an Arlington, VA, water pollution treatment plant and was incubated with 5 ppm diphenylamine; results from three separate test runs were virtually identical. In a 24-hour incubation period, >96% of the diphenylamine was degraded with ~65% degraded within the first 6 hours. Control tests using sterilized activated sludge produced no significant degradation, indicating that degradation in the non-sterilized sludge was microbial. Metabolites of the degradation were identified via GC/MS as 4-hydroxydiphenylamine, aniline, indole and an isomer of 4-hydroxydiphenylamine. Furukawa et al. (1978) used the Warburg technique to test the degradation of diphenylamine in two bacterial strains, Alcaligenes Y42 and Acinetobacter P6, and found no degradation. Ayanaba and Alexander (1973) tested 25 microorganisms for their ability to nitrosate diphenylamine in the presence of nitrite. Ten of the microorganisms (obtained from lake water, garden soil, sewage, cow manure and stock cultures) were found to generate N-nitrosodiphenylamine after 2-10 days of incubation with 0.5% diphenylamine in mineral salts medium at a pH of 7.

The chemical degradation of diphenylamine in the aquatic environment has received little attention in the available literature. The chemical reactivity of diphenylamine suggests that some chemical reactions may occur. Rao and Hayon (1975) have determined a rate constant for the reaction of OH radicals with diphenylamine in water to be 1.5×10^9 M^{-1} sec^{-1}; assuming an environmental OH• concentration of 10^{-17} M, a half-life of 530 days can be calculated, which is not very significant. Various

other oxidants such as the alkyl peroxyl radicals ($RO_2\cdot$) can be generated in the aquatic environment by photochemical means. The RO_2 radicals can then chemically react with pollutants present in aquatic media (Mabey et al., 1981). Mabey et al. (1981) found that reaction of $RO_2\cdot$ with aromatic amines can occur quite rapidly in the aquatic environment (half-life of less than several days). Experimental data specific to diphenylamine are not available. The U.S. EPA-NIH (1984) reported that an aqueous solution of diphenylamine will turn yellow in 3-5 days. This decomposition may result from photolytic, chemical, or a combination of chemical and photolytic reactions. Laughlin et al. (1983) reported that a wet air oxidation process (duration of treatment unavailable in the abstract of this study) for treating wastewaters is totally effective in removing diphenylamine.

The transport of diphenylamine in the aquatic environment will depend on the ability of the compound to volatilize, to adsorb to particulate matter and sediment and to bioaccumulate in aquatic organisms. Volatilization is related to the vapor pressure and water solubility of a compound. Vapor pressure data for diphenylamine in the solid-phase at 20°C were not available; however, from the available data, the vapor pressure of diphenylamine can be extrapolated to lower temperatures by the method suggested by Mabey et al. (1981). At the melting point (53°C), the extrapolated vapor pressure is ~0.035 mm Hg and the estimated vapor pressure of super-cooled liquid diphenylamine at 20°C is ~0.0025 mm Hg. In the solid-phase at 20°C, the vapor pressure of diphenylamine can be calculated to be ~0.001 mm Hg. The water solubility data reported in Section 1.2. is not consistent at 20-25°C, with a reported range of 29.6-300 ppm. The data reported by Hashimoto et al. (1982), however, were determined by two different experimental solubility measuring techniques and seem to be the most acceptable data reported;

therefore, the water solubility of diphenylamine at 20°C will be considered to be ~50 ppm. Assuming this water solubility and the calculated vapor pressure of solid-phase diphenylamine at 20°C, the Henry's Law constant can be calculated to be 4.5×10^{-6} atm-m³/mol. This value of Henry's Law constant indicates that environmental volatilization will be slow (Lyman et al., 1982). No experimental aqueous evaporation studies are available for this compound.

The adsorption of diphenylamine to particulate organic matter and sediment in the aquatic environment may be predicted from K_{om} and K_{oc} values. Briggs (1981) experimentally determined a K_{om} value for diphenylamine in four silt loam soils (organic matter content of 1.09-4.25%) to be ~350. In addition, K_{oc} value estimates can be >1000 (Section 2.3.). These K_{om} and K_{oc} values indicate that diphenylamine has a medium-to-low mobility in soils; therefore, some partitioning of diphenylamine between the water and sediment matrices of the aquatic environment may occur. The quantitative significance of adsorption is difficult to ascertain without experimental investigation; however, Akiyama et al. (1980) detected dephenylamine in river sediment in Japan.

Veith et al. (1979) experimentally measured the bioconcentration of diphenylamine in fathead minnows using a 32-day exposure flow-through aquarium at a mean diphenylamine concentration of 43.7 ppb. At the conclusion of the test period, the BCF of diphenylamine in the fathead minnows was determined to be 30, which is not indicative of significant bioaccumulation. Kawasaki (1980) reported that the MITI test predicts a BCF of ~100 in fish, while Sasaki (1978) reported that the MITI test predicts that diphenylamine may be moderately bioaccumulative. The bioconcentration potential can be estimated from K_{ow} data with the following equation (Veith et

al., 1980): Log BCF = 0.76 Log K_{ow} - 0.23. This equation predicts a BCF value of 226 when Log K_{ow} is 3.4. Estimation of BCF can also be done from WS with the following equation (Kenaga, 1980): Log BCF = 2.791-0.564 Log WS. This equation predicts a BCF value of 68 when the WS is 50 ppm. None of the experimental data or estimations suggest that diphenylamine will be strongly bioaccumulated. Konasewich et al. (1978) detected diphenylamine in fish in the Great Lakes; however, concentrations or other relevant test data were not reported.

2.2. AIR

The atmospheric chemical removal processes include photolytic transformations, reaction with hydroxyl and other radicals, and reaction with ozone. As noted in Section 2.1., diphenylamine can undergo direct photolysis in the environment, as it absorbs significant UV radiation in the range of 290-310 nm. Photolysis rate data under simulated atmospheric conditions are not available, however, to determine the significance of atmospheric photolysis. Pertinent data are also not available which consider the possible atmospheric radical or ozone reactions of this compound.

The physical atmospheric removal processes include dissolution, adsorption on aerosol particles and deposition. Lunde et al. (1977) detected diphenylamine in the particulate part of rainwater collected in Norway, which suggests that wet deposition may be significant. Cupitt (1980) derived an equation that predicts a dissolution half-life of a chemical in the atmosphere assuming an annual rainfall of 0.75 m and a homogeneous atmosphere of 8 km height. For diphenylamine, the dissolution half-life is calculated to be ~1.3 years. Adsorption on aerosol particles is only important when the saturation vapor pressure is $<10^{-7}$ mm Hg (Cupitt,

1980); for diphenylamine, adsorption is therefore not important. Dry deposition is probably insignificant. The study of Lunde et al. (1977) suggests that diphenylamine may undergo long distance transport in the atmosphere.

2.3. SOIL

As noted in Section 2.1., diphenylamine has been shown to be degradable by various microorganisms, including microorganisms obtained from soil. Additional quantitative soil microbial degradation studies were not located; therefore, it is difficult to estimate the importance of microbial decomposition of diphenylamine in the natural soil environment. Piet and Morra (1983) found that passing Rhine river water, containing 1 ppb diphenylamine, through the soil of a bank filtration system results in the disappearance of diphenylamine, which may be attributable to microbial or chemical degradation, or to adsorption.

The photolytic decomposition of diphenylamine on soil surfaces is possible, although this mechanism has not been investigated experimentally.

Briggs (1981) measured the K_{om} of diphenylamine in four silt loam soils (organic matter content 1.09-4.25%) to be ~350. This indicates that diphenylamine has a moderate soil mobility in the soils tested. The K_{oc} values can be estimated from the following equations, using WS and K_{ow}:

$$\text{Log } K_{oc} = 3.64 - 0.55 \text{ Log WS (in ppm)} \quad \text{(Kenaga, 1980)} \qquad (2\text{-}1)$$

$$\text{Log } K_{oc} = 0.44 - 0.54 \text{ Log WS (in mole fraction)} \quad \text{(Karickhoff et al., 1979)} \qquad (2\text{-}2)$$

$$\text{Log } K_{oc} = 0.544 \text{ Log } K_{ow} + 1.377 \quad \text{(Kenaga, 1980)} \qquad (2\text{-}3)$$

$$\text{Log } K_{oc} = 1.00 \text{ Log } K_{ow} - 0.21 \quad \text{(Karickhoff et al., 1979)} \qquad (2\text{-}4)$$

The K_{oc} values obtained from equations 2-1 through 2-4 are ~500, 1940, 1680 and 1550, respectively. These values predict a low to moderate mobility of diphenylamine in soil.

Pertinent data regarding the volatilization of diphenylamine from soil surfaces were not located in the available literature as cited in the Appendix. The relatively low vapor pressure and moderately high K_{oc} values suggest that soil volatility may not be important. Its expected low volatility from water also predicts low volatility from soil.

3. EXPOSURE

3.1. WATER

The gross analysis data from the U.S. EPA STORET data base contains 152 observations for diphenylamine with a mean concentration of 5 µg/ℓ and a range of 3.2-10.0 µg/ℓ.

In a project initiated by the Health Effects Research Laboratory of the U.S. EPA, Pahren and Melton (1979) reported the presence of trace organics in effluents from advanced water treatment plants. Diphenylamine was detected in the effluent from a Lake Tahoe plant at a concentration of 1.54 ppt and in the effluent from a Pomona, CA, plant at a level of 9.77 ppt. Ellis et al. (1982) detected diphenylamine (no concentrations reported) in the effluent from a publicly-owned treatment facility at Sauget, IL.

Piet and Morra (1983) monitored the levels of organics in polluted surface waters in the Netherlands in relation to their disappearance by use of bank filtration as a cleanup method for drinking water. Diphenylamine was detected in raw Rhine water at a level of 1 ppb, but was not detected in tap water after passage through the bank filtration system. Akiyama et al. (1980) detected diphenylamine (no concentration reported) in river sediment in Japan. Lunde et al. (1977) detected diphenylamine (no concentration reported) in rainwater in Norway.

The leaching of diphenylamine from rubber products has been observed by several investigators. Danielson et al. (1983) identified diphenylamine in leachate from rubber stoppers using parenteral solutions, while Babish et al. (1983) noted the extraction of diphenylamine in aqueous extracts from rubber nursing nipples. The leaching of diphenylamine from rubber products

containing a diphenylamine antioxidant suggests that these types of rubber products, when landfilled, may leach from soil into groundwater, particularly from soils with low adsorption capacity.

3.2. FOOD

Duggan et al. (1983) reported pesticide residue levels that were monitored in American foods by three Federal programs during the fiscal years 1970-1976. The three programs are the Total Diet Program, administered by the FDA on ready-to-eat foods; FDA's Monitoring Program for raw agricultural commodities, which examined 33,000 domestic and >18,000 imported samples; and the USDA's National Residue Program, which examined >15,000 red meats and 11,000 poultry samples. Diphenylamine was detected in only one sample of fruits and in only one sample of infant and junior foods; no concentrations were reported.

As noted in Section 1.4., diphenylamine and wrapping papers treated with diphenylamine can be used as a preservative in apple and pear storage. The commercial importance of this storage method is not clear; however, apples and pears that are treated in this manner are likely to contain residues. Monitoring data for diphenylamine residues in apples were not located.

Konasewich et al. (1978) found diphenylamine (no concentration or sampling date reported) in fish in the Great Lakes.

Babish et al. (1983) analyzed aqueous extracts from four brands (eight types) of rubber nursing nipples purchased in the open market for selected volatile organics. Diphenylamine was found to be released continuously into aqueous extracts from most brands. As noted in Section 1.4., diphenylamine and its derivatives are used widely as antioxidants in rubber and polymer products.

3.3. INHALATION

Pellizzari (1978) monitored the ambient air in Geismar, LA, for several organic compounds, but detected only trace amounts (not quantified) of diphenylamine in a few samples.

The presence of diphenylamine in rainwater in Norway (Lunde et al., 1977) suggests the existence of diphenylamine in some ambient airs.

3.4. DERMAL

Pertinent data regarding dermal exposure to diphenylamine were not located in the available literature as cited in the Appendix.

4. PHARMACOKINETICS

4.1. ABSORPTION

Although quantitative data regarding the absorption of diphenylamine were not available, gastrointestinal absorption of diphenylamine can be inferred from systemic toxicity observed in laboratory animals following oral exposure to the chemical (Section 5.5.).

Pertinent data regarding the absorption of diphenylamine by the dermal or inhalation routes were not located in the available literature as cited in the Appendix.

4.2. DISTRIBUTION

Pertinent data regarding the distribution of diphenylamine were not located in the available literature as cited in the Appendix.

4.3. METABOLISM

Rats given single intraperitoneal injections of 5 mg of unlabeled diphenylamine in propylene glycol produced the urinary and biliary metabolites, 4-hydroxy and 4,4'-dihydroxy diphenylamine, identified chromatographically (Alexander et al., 1965). Unchanged diphenylamine and its 4-hydroxy, 4,4'-dihydroxy, and 2-hydroxy derivatives were found in the urine of a rabbit treated orally with 5 g aqueous diphenylamine. O-Sulfate and O-glucuronide (as the tri-O-acetylmethyl ester) conjugates of 4-hydroxy diphenylamine were also isolated (Alexander et al., 1964, 1965).

Metabolites of diphenylamine after ingestion by humans were found in urine (Alexander et al., 1965). These were 4-hydroxy and 4,4'-dihydroxy derivatives, and also unchanged diphenylamine. No N-hydroxylated derivatives were detected.

Dogs given diphenylamine in the diet at a concentration of 1% for a period of 2 years produced 4-hydroxy, its sulphate and N-glucosiduronide

derivatives, and 4,4'-dihydroxydiphenylamine (De Eds, 1963). These metabolites were also detected by Booth (1963) in dog and rat urine after administration of diphenylamine. De Eds (1963) also reported that 4-hydroxy diphenylamine was formed following *in vitro* incubation of diphenylamine with rat liver.

Galea et al. (1975) found nitrosodiphenylamine in the stomach contents of rats that received an oral dose of 5 mg diphenylamine combined with 10 mg nitrite ($NaNO_2$). Sander et al. (1968, 1974) also demonstrated the synthesis of nitrosamines in the stomach of rats given diphenylamine along with a solution of $NaNO_2$ in the diet. Challis and Kyrtopoulos (1977) found that N-nitrosamines were formed more rapidly when diphenylamine was reacted with N_2O_4 in neutral or alkaline aqueous solution than when diphenylamine was reacted with $NaNO_2$ in acidic media. The reaction of diphenylamine with N_2O_4 to produce the N-nitrosamine also occurred when either plasma or whole blood was substituted for the aqueous solvent. Nitrosodiphenylamine has been demonstrated to be a carcinogen (NCI, 1979).

4.4. EXCRETION

Excretion studies were done in the rat by Alexander et al. (1965). Male rats received 5 mg/kg of ^{14}C-diphenylamine intraperitoneally and urine was collected at 24-hour intervals. After 48 hours, 75% of the administered dose of radioactivity appeared in the urine. Male rats with cannulated bile ducts received 5 mg/kg of ^{14}C-diphenylamine by slow intravenous injection (an aqueous 50% ethanol solution containing 2 mg/mL). Bile samples were collected at 1-hour intervals. Of the administered radioactivity 25% was excreted in the bile after 6 hours.

5. EFFECTS

5.1. CARCINOGENICITY

As reviewed by FAO/WHO (1976), Coulston et al. (1971) maintained "groups of 100-200 mice of each sex" on diets containing diphenylamine (99.5% pure) at 0, 50, 100 and 250 ppm (0, 0.005, 0.01 and 0.025%) for up to 92 weeks. Interim kills of unspecified numbers of mice were performed at 6, 12 and 18 months. Histopathological examination of unspecified organs and tissues revealed no increased tumor incidence or rate of tumor formation between treated groups and controls. This study is summarized in Table 5-1.

Thomas et al. (1967a) found no increased incidence of benign or malignant tumors at autopsy and histologic examination of major organs after 2 years of feeding diphenylamine at concentrations of 0.0, 0.001, 0.01, 0.10, 0.50 and 1% (Table 5-2). For each dietary concentration, there were 20 male and 20 female weanling albino rats of the Slonaker-Addis strain. The authors attributed tumor incidences to senility and aging; incidences were not increased over controls. Autopsies were performed on the 734th day. Survivor figures for the 640th and 734th days are presented in Table 5-3.

Griswold et al. (1966) found no neoplastic changes in 20 female Sprague-Dawley rats treated with a single gavage dose of diphenylamine in oil at the predetermined MTD of 300 mg/rat, and observed for the next 6 months (Table 5-4). A group of 89 female rats served as vehicle controls. The rats were ~50-55 days of age when treated. All rats that died or were sacrificed were examined for gross lesions, and histologic examination of major organs was performed. Mortality at 6 months was 2/20 for treated rats and 5/89 for control rats.

TABLE 5-1

Summary of Dietary Carcinogenicity Study in Mice*

Exposure Route	Species/ Strain	Sex	Dietary Concentration ppm	Duration of Treatment	Duration of Study	Purity of Compound (%)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
Oral	mouse/NR	M + F	0 50 (0.005%) 100 (0.01%) 250 (0.025%)	92 weeks	92 weeks	99.5%	diet	NA	NA	NA

QUALITY OF EVIDENCE

Strengths of Study: Both sexes of mice were treated at three dosage levels for a significant portion of their lifespan. The compound was relatively pure. A large number of mice per group (100-200) was studied. Interim kills were preformed at 6, 12 and 18 months.

Overall Adequacy: Adequate

*Source: Coulston et al., 1971

NA = Not applicable

NR = Not reported

TABLE 5-2

Summary of Dietary Carcinogenicity Study in Rats*

Exposure Route	Species/ Strain	Sex	Dietary Concentration (%)	Duration of Treatment	Duration of Study	Purity of Compound (%)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
Oral	rat/ Slonaker-Addis	M	0.0 0.001 0.01 0.10 0.50 1.0	730 days	730 days	99.9	diet	NA	NA	NA
		F	0.0 0.001 0.01 0.10 0.50 1.0							

QUALITY OF EVIDENCE

Strengths of Study: Several dose levels, both sexes; 2-year duration; adequate number of animals tested, 20 for each dose percentage

Overall Adequacy: Adequate

*Source: Thomas et al., 1967a

NA = Not applicable

TABLE 5-3

Number of Rats Surviving at 640 and 734 Days of Feeding of Diphenylamine[a]

Concentration of Diphenylamine in Diet (%)	Males[b]		Females[b]	
	640 days	734 days	640 days	734 days
Control	13	13	14	11
0.001	12	12	12	9
0.01	15	15	18	15
0.10	15	14	17	11
0.50	12	12	12	9
1.0	13	10	12	11

[a]Source: Thomas et al., 1967a

[b]The study commenced with 20 males and 20 females.

TABLE 5-4

Summary of Gavage Carcinogenicity Study in Rats*

Exposure Route	Species/Strain	Sex	Dose	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (%)
Oral	rat/ Sprague-Dawley	F	300 mg/rat	one dose via gastric tube	6 months of observation	commercial grade	sesame oil	NA	NA	NA

QUALITY OF EVIDENCE

Strengths of Study: 20 rats tested; sesame oil controls used for negative control, DMBA-fed positive control used; all organs observed at autopsy and histology done; only 2/20 treated rats dead at 6 months

Weakness of Study: One dose; relatively short-term study; only one sex; only one species

Overall Adequacy: Limited

*Source: Griswold et al., 1966

NA = Not applicable

Hiasa et al. (1982) observed renal tumors in rats treated with N-ethyl-N-hydroxyethylnitrosamine, using diphenylamine as a promotor. Further details were not provided in the abstract of this Japanese study.

In a combined *in vitro*/*in vivo* bioassay for neoplastic transformation, DiPaolo et al. (1973) treated pregnant Syrian Golden hamsters intraperitoneally with diphenylamine at 0.5-2.0 mg/100 g bw (5-20 mg/kg bw) on day 10 or 11 of gestation. On day 13 of gestation, the fetuses were excised, and cell cultures were prepared from the whole fetus, passaged several times and scored for evidence of transformation. In addition, the fetal cells were injected subcutaneously into weanling male hamsters that had been given 450 R of X-irradiation and observed for tumor development for a minimum of 1 year. Negative results were obtained for diphenylamine in these assays; positive results were obtained with known carcinogens.

Although diphenylamine has not been demonstrated to be carcinogenic, N-nitrosodiphenylamine, which can be formed in the stomach by the reaction of diphenylamine with nitrite (see Section 4.3.), induced transitional cell carcinomas of the urinary bladder in male and female F344 rats (NCI, 1979). N-nitrosodiphenylamine was not found to be carcinogenic for $B6C3F_1$ mice of either sex, or in C57Bl mice (IARC, 1982). The subject of secondary and tertiary amines tested in combination with nitrite for carcinogenic activity in long-term animal studies was reviewed by Mirvish (1975).

It should also be noted that 4-aminobiphenyl, a common impurity in diphenylamine, is a carcinogen (IARC, 1972; Parkes, 1976).

5.2. MUTAGENICITY

The results of mutagenicity testing of diphenylamine are summarized in Table 5-5.

TABLE 5-5

Mutagenicity Testing of Diphenylamine

Assay	Indicator/ Organism	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	Salmonella typhimurium TA1538	plate incorporation	100 µg/plate	±S-9	-	NC	Ferretti et al., 1977
Reverse mutation	S. typhimurium G46 TA1535 TA1000 C3076 TA1537 D3052 TA1538 TA98	plate incorporation	10,000-fold concentration range/	±S-9	-	negative in all strains	Probst et al., 1981
Reverse mutation	S. typhimurium TA98 TA100 TA1535 TA1537	spot test	3 µmol/plate	±S-9	-	negative in all strains; diphenylamine precipitated on the plate, making evaluation of results difficult	Florin et al., 1980
Reverse mutation	S. typhimurium TA98 TA1538	plate incorporation	NR	±S-9	-	when tested for comutagenicity with norharman, there was a positive response in the presence, but not absence, of S-9 in TA98	Sugimura et al., 1982
Reverse mutation	S. typhimurium TA98 TA100	plate incorporation	NR	±S-9	-	when tested for comutagenicity with norharman, there was a positive response in the presence, but not absence, of S-9 in TA98	Wakabayashi et al., 1982
Reverse mutation	Escherichia coli WP2 WP2uvrA⁻	plate incorporation	10,000-fold concentration range/plate	±S-9	-	negative in both strains	Probst et al., 1981
Forward mutation	L51784 mouse lymphoma TK⁺/⁻ cells	to cells in in suspension	0 and 3.79×10^{-5} to 28.49×10^{-5}M	S-9	-	NC	Amacher et al., 1980
Unscheduled DNA synthesis	adult F344 rat hepatocytes	cell culture	100 nmol/ml	NA	-	NC	Probst et al., 1981

NC = No comment; NR = Not reported; NA = Not available

Diphenylamine was negative for reverse mutation in the presence and in the absence of S-9 metabolic activation when tested by spot test or plate incorporation in Salmonella typhimurium strains TA98, TA100, TA1000, TA1535, TA1537, TA1538, C3076, D3052 and G46 (Ferretti et al., 1977; Probst et al., 1981; Florin et al., 1980; Sugimura et al., 1982; Wakabayashi et al., 1982) and in Escherichia coli strains WP2 and WP2uvrA$^-$ (Probst et al., 1981). Negative results were also obtained for forward mutation in the thymidine kinase locus of cultured L51784 mouse lymphoma cells in the presence of S-9 (Amacher et al., 1980) and for unscheduled DNA synthesis in cultured rat hepatocytes (Probst et al., 1981).

In addition to the data presented in Table 5-5, diphenylamine at 2.5-20 µg/mL caused no significant increase in the transformation of normal rat kidney cells by murine sarcoma virus, with or without metabolic activation by rat liver S-9 fraction (Wilson and Khoobyarian, 1982).

Sugimura et al. (1982) and Wakabayashi et al. (1982) tested the comutagenicity of diphenylamine with norharman, a component of cigarette smoke, in S. typhimurium strain TA98. Neither diphenylamine nor norharman alone was mutagenic in the presence or absence of S-9. When tested in combination, however, a significant increase in the number of revertants/µmol was observed in the presence of S-9.

N,N-Diphenylnitrosamine, a known carcinogen that can be formed in the stomach by the reaction of diphenylamine with nitrites (see Section 4.3.), was mutagenic to Salmonella typhimurium TA98 in the presence of S-9 mix and the comutagen, norharman. S-9 mix was required for the comutagenic action of norharman. Diphenylamine was more mutagenic in the presence of norharman and S-9 mix than diphenylnitrosamine, suggesting the diphenylnitrosamine yields diphenylamine metabolically and then exerts comutagenesis with

norharman (Sugimura et al., 1982; Wakabayashi et al., 1982). N-nitroso-diphenylamine was not mutagenic in reverse mutation assays without norharman in other studies (McCann et al., 1975; Yahazi et al., 1977; Araki et al., 1984). N-Nitrosodiphenylamine has been tested extensively in short-term assays in prokaryotes and eukaryotes for mutagenicity and other chromosomal effects. It was not mutagenic and did not induce unscheduled DNA synthesis or chromosomal damage under any test condition employed (IARC, 1982). Negative results were obtained for reverse mutation in S. typhimurium strain TA1940 in a host-mediated assay in which mice were treated intraperitoneally with diphenylamine and simultaneously by gavage with sodium nitrite (Braun et al., 1977).

5.3. TERATOGENICITY

Pregnant Sprague-Dawley (Simonsen) rats were fed diphenylamine, and their newborn offspring were histologically evaluated for cystic kidney changes (Crocker et al., 1972). Two experimental groups were studied: group I was given chromatographically purified components of commercial diphenylamine in 2 mℓ of 70% alcohol via stomach tube daily for 7 days prior to delivery and group I was fed diphenylamine in the diet at concentrations of 1.5 or 2.5% for the last 7 days of gestation. Further details and dosages are presented in Table 5-6. It should be noted that in both groups I and II the number of offspring per litter varied from 3-17 and that there was a high degree of cannabalism of the newborns by the mothers of some litters. No statistical evaluation was made of this event. Cystic lesions were seen in the proximal nephrons of newborn rats exposed in utero to commercial diphenylamine, with severity depending upon the commercial source and age of the compound. Diphenylamine from Eastman Chemical Co., aged for 2 years, had the most severe effect. When the diphenylamine was

TABLE 5-6

The Incidence of Cystic Renal Disease in Neonatal Rats Exposed to Diphenylamine *In Utero*[a]

Chemical	Method of Administration	Daily Dose/ Dietary Concentration	No. Pregnant Rats Treated		No. of Newborn Rats with Histologic Changes[b]			
			Delivered	Failed[c]	Negative	Mild	Moderate	Severe
DPA-K[d], aged 2 years[e]	gavage, daily in 2 mL 70% EtOH	20 mg	18	3	8	6	21	4
DPA-E, purified[f]		20 mg	20	0	26	6	0	0
Contaminant E[g]		50 µg	36	8	18	4	30	0
Contaminant F[g]		50 µg	11	2	18	0	0	0
Contaminant G[g]		50 µg	6	1	12	8	0	0
Control, 70% alcohol		NA	11	3	24	0	0	0
DPA-K[d], aged 2 years[e]	oral in diet	1.5%	8	4	4	4	0	0
DPA-K[d], aged 2 years[e]		2.5%	27	10	0	13	31	6
DPA-K[d], aged 3 months[e]		2.5%	5	0	10	6	0	0
DPA-B[h], aged 2 years[e]		2.5%	6	2	20	10	4	0
Control, *ad libitum* powdered chow		0.0%	7	2	12	0	0	0

[a]Source: Crocker et al., 1972

[b]Graded severity of cystic tubular dilation observation in histological section of newborn rat kidneys.

[c]Failed to deliver viable young or mother died

[d]DPA-K indicates commercial diphenylamine supplied by Eastman Chemical Co.

[e]Estimated minimal shelf age of commercial diphenylanine

[f]Diphenylamine isolated from contaminant by TLC

[g]Isolated bands from TLC

[h]DPA-B indicates commercial diphenylamine supplied by Baker Chemical Co.

NA - Not applicable

chromatographically purified, the severity of the lesions in the newborn rats was greatly reduced. At no time were any of the dams affected by administration of the chemical; histology of the kidneys was normal in both groups. Lesions in the newborn rats were also seen with one of the purified contaminants (see Table 5-6). These authors concluded that purified diphenylamine is not the nephrotoxic component of commercial diphenylamine, and that a contaminant, compound E, was the chemical responsible for the effect. The concentration of this component was suspected to increase upon aging of diphenylamine, since aged crude diphenylamine produced a high incidence of cystic dilation in newborn rats, whereas recently manufactured diphenylamine was less nephrotoxic. Abnormalities of the proximal nephron were induced in the fetal kidney by relatively brief exposure of the dam, as compared with several months of feeding required to induce a similar lesion in adult rats (Section 5.5.). These authors also described other studies which indicated that variations in timing of feeding of diphenylamine to pregnant rats resulted in differences in the site of the lesions in the fetal developing kidney.

An earlier study, reported in abstract form (Crocker and Vernier, 1970), demonstrated polycystic changes in newborn rats from dams fed diphenylamine at a concentration of 2.5% in the diet or given 2 ml of 1% diphenylamine in alcohol via tube feeding for the last 6 days of pregnancy. Controls received a diet without diphenylamine or were tube fed alcohol. All 70 of the newborn rats showed such kidney abnormalities as cystic dilation of the collecting ducts and vacuolar degeneration of the proximal tubules. Further details on newborn kidney and microdissection observations were provided by these authors.

5.4. OTHER REPRODUCTIVE EFFECTS

Groups of Slonaker-Addis albino rats, 12 females and 3 males each 5 weeks of age, were fed diets containing 99.9% pure diphenylamine at levels of 0.0, 0.1, 0.25 and 0.50% at 5 weeks of age, dietary level (Thomas et al., 1967a; De Eds, 1963). Animals were mated at 100 days, and the litters that were produced were mated once. After the first litters produced were weaned, the parental group in the study was remated. Results are presented in Table 5-7. In general, as dietary concentration of diphenylamine increased, average size of litters decreased, except for numbers of pups born and weaned in the second generation whose dams were fed the 0.1% diet. The dams' food consumption was not measured, but gestating and lactating rats fed 0.5% diphenylamine probably consumed less food in the same manner as seen in the growth inhibition study presented by these investigators (Thomas et al., 1967a). In this study, growth inhibition occurred in rats fed at dietary concentrations of 0.5 and 1.0% diphenylamine for 730 days (Section 5.5.) and was correlated with decreased food intake. Food consumption (g/rat/day) for both males and females was depressed significantly ($p<0.01$) at these levels, compared with all the other lower concentrations. The authors attributed effects on reproduction to inadequate food intake.

5.5. CHRONIC TOXICITY

The effects of oral administration of diphenylamine to rats have been investigated by Thomas et al. (1957, 1967a); Darmady et al. (1965, 1970); Kime et al. (1962); De Eds (1963); Safouh et al. (1970); Gardner et al. (1976); Eknoyan et al. (1976); Evan and Gardner (1976); Evan et al. (1978); and Woodhouse et al. (1965). Studies using diphenylamine were also done in mice (Coulston et al., 1971; 1972) dogs (De Eds, 1963; Thomas et al., 1967b), and guinea pigs (Philbert et al., 1979). Details and results of these studies are summarized in Table 5-8. Reviews of diphenylamine-induced

TABLE 5-7

Reproduction Performance of Rats Fed Diphenylamine[a]

Concentration of Diphenylamine in Diet (%)	No. of Females	Born		Weaned		Mean Weight at Weaning (21 days)	
		No. of Litters	Mean No./ Litter	No. of Litters	Mean No./ Litter	Males (g)	Females (g)
First mating (December to February, 63 days)							
Controls	12	12	8.3	10	7.5	29.6	27.8
0.10	12	10	9.0	10	8.3	31.9	28.7
0.25	12	10	6.8	9	7.1	29.9	27.8
0.50	12	10	6.3[b]	8	6.3	26.9	25.8
Second mating (March to May, 63 days)							
Controls	12	9	9.6	9	9.3	28.3	27.5
0.10	12	12	7.3[b]	11	7.1	37.0	36.0
0.25	12	12	7.3[b]	12	7.3	35.5	34.4
0.50	12	11	6.6[c]	11	6.6	28.2	28.2
Second generation (May to July, 63 days)							
Controls	12	10	8.6	10	8.5	31.0	30.6
0.10	11[d]	11	5.8[c]	11	5.7[c]	31.1	31.2
0.25	12	12	7.3	12	7.0	30.0	29.3
0.50	12	11	7.0	11	6.6	24.9[c]	24.8[c]

[a]Source: Thomas et al., 1967a

[b]Shown significantly lower than control value at 5% level ($p<0.05$)

[c]Shown significantly lower than control value at 1% level ($p<0.01$) by method of Duncan (1955)

[d]One female died during the first week.

TABLE 5-8

Effects of Diphenylamine*

Species/Strain	Sex/No.	Weight/Age	Compound or Purity	Dose/ Concentration	Duration	Effects	Reference
Rats/Slonaker-Addis	F/NR	NR/NR	diphenylamine/ NR	0.025, 0.1, 0.5, 1.0 or 1.5%	226 days	Toxic effects only at ≥0.5% level; included growth inhibition, renal tubule dilatation, suggestion of blood destruction.	Thomas et al., 1957
Rats/Sprague-Dawley	M/11 NR/7 3 control groups: NR/10 NR/7 NR/7	250 g/adult NR/weanling adult adult weanling	diphenylamine/ technical grade	2.5% 2.5% 0% 0% 0%	365 days 365 days	Morphological alterations of renal tubules in all animals, tubular dilatation to overt cyst formation within 47 days, severity of effect proportional to duration of treatment; proximal tubular proliferation and degeneration, cytoplasmic swelling of distal tubules, narrowing of tubular amina; decrease in renal clearance values (glomular filtration rate and maximum urinary osmolality); increased susceptibility to pyelonephritis; no proteinuria or glycosuria, all other organs appeared normal histologically.	Kime et al., 1962
Rats/NR	M/NR	NR/weanling	diphenylamine/ NR	2.5%	133 days	Kidney changes by 6 weeks; proximal tubule epithelial cell changes; distal tubule degeneration; vacuolization; swollen mitochondria; epithelial sloughing, leaving naked thickened basementmembrane; replacement of tubular epithelium with fibroblasts; cyst formation.	Woodhouse et al., 1965; Darmady et al. 1965; 1970
Rats/Slonaker-Addis	M/20 F/20 for each percentage tested	~40 g NR/weanling	diphenylamine/ 99.9% pure	0.0, 0.001, 0.01, 0.10, 0.50 or 1.0%	730 days	Growth arrest for both sexes at 0.5 and 1%; significant depressed average weight for females at 0.10% ($p<0.01$); lower food consumption at 0.5 and 1%, slightly depressed hemoglobin at 1%, returning to normal when diphenylamine removed from diet; cystic dilatation and chronic nephritis between levels 0.1 and 0.5%, no glycosuria or proteinuria; some hyperplasia in bladder in males at 1%. No adverse effects at ≤0.01%.	Thomas et al., 1967a; De Eds, 1963

TABLE 5-8 (cont.)

Species/Strain	Sex/No.	Weight/Age	Compound or Purity	Dose/ Concentration	Duration	Effects	Reference
Rats/Sprague-Dawley	NR/60 NR/40 NR/10 NR/10 NR/10 NR/20	200-350 g/NR	diphenylamine/ NR	2.5% 1.5% 2.5% + 0.25% sulfur-containing amino acids 1.5% + 0.25% sulfur-containing amino acids 0.5% + 0.25% sulfur-containing amino acids 0%	365 days 365 days 365 days 365 days 365 days (sacrificed at 2-month intervals)	Histologic defects dependent on length of administration with both concentrations, more severe with higher concentration of diphenylamine; trend analysis showed direct relationship between dose dose administered and degree of cystic changes, but some variance due to other factors; at 2 months, cystic changes of grades 1 and 2 severity occurred in 6/8 rats fed 2.5% diphenylamine; changes were more severe when sulfur-containing amino acids fed with diphenylamine at 1.5+2.5% level; 10 animals fed diphenylamine plus amino acids were normal after 6 months feeding; marked reduction in weight gain; spleen enlargement and severe hemolytic anemia with hemoglobinuria at 2.5% level of feeding.	Safouh et al., 1970
Rats/Sprague-Dawley	F/NR	70-90 g/NR	diphenylamine/ NR	0 or 2.5%	3-6 weeks	Defect in maximum urine concentrating ability by 2nd week, 50% of control values, gross cysts in 10%; structural changes in collecting ducts; histological alterations in all treated animals in kidneys.	Eknoyan et al., 1976
Rats/Sprague-Dawley	M/3 3 male controls	NR/NR	diphenylamine/ NR	0 or 1%	365-547 days	Cysts along the nephrons and collecting ducts structural changes seen with electron microscopy.	Evan and Gardner, 1976
Rats/Sprague-Dawley	M/NR	75-100 g	diphenylamine/ commercial grade	0 or 1%	5-20 months	Cystic kidney changes with variably severe and frequently incomplete tubular occlusion; after 5-11 months kidneys were precystic with less marked tubule alterations; at 12-20 months kidneys were cystic with dilated tubules; no significant difference in kidney-to-body weight ratios were found when diphenylamine-fed animals were compared to controls.	Gardner et al., 1976
Rats/Sprague-Dawley	M/25 per group	300-420 g NR	diphenylamine/ commercial grade	0 or 1%	rats examined at 2, 4, 5, 10, and 20 weeks	Hyperplasia of kidney; at 5 weeks, hyperplastic change of medullary collecting ducts and defect in urinary concentrating ability; at 10 weeks, collecting tubules showed dilation with a few necrotic cells later on; nephron showed cystic change.	Evan et al., 1978

TABLE 5-8 (cont.)

Species/Strain	Sex/No.	Weight/Age	Compound or Purity	Dose/ Concentration	Duration	Effects	Reference
Rats/NR Guinea pigs/NR	NR/NR	NR/NR	diphenylamine/ NR	2 or 4%	NR	With 2% level, 10% of animals died within 6 months; with 4% level, 60% of animals died within 6 months; tubular nephritis, cystic dilations in kidney, vacuolar degeneration and necrosis of hepatocytes in liver; lungs showed capillary congestion, edema and inflammatory lesions; guinea pigs were more sensitive, showing increased cyst formation frequency.	Philbert et al., 1979
Mice/NR	M and f/ 100-200 per group	NR/NR	diphenylamine/ 99.5%	0, 50, 100 and 250 ppm (0, 0.005, 0.01 and 0.025%)	up to 92 weeks with interim kills at 6, 12 and 18 months	No effects on growth, mortality, hematologic indices or incidence of histologic changes; dose-related increase in Heinz bodies in red blood cells at 92 weeks at $\geq$50 ppm; spleen weight of both sexes increased 12 and 18 months at 250 ppm; increased hemosiderosis in spleens and increased number of reticulocytes in blood at 6 and 12 months at 250 ppm.	Coulston et al., 1971
Mice/NR	M and f/ 50-100 per group	NR/NR	diphenylamine/ NR	0, 5, 10, 50, 100, 250 and 1000 ppm (0.0005, 0.001, 0.005, 0.01, 0.025 and 0.1%)	6 months	Heinz bodies observed in erythrocytes of mice at $\geq$50 ppm, with maximum numbers at days 9-30; Heinz bodies decreased with time, thereafter.	Coulston et al., 1972
Dogs/beagle	M/2 f/2 per group	7-8 kg/ 8 months	diphenylamine/ 99.9%	0, 0.01, 0.10 and 1%	737 days	Fatty change in liver, hemosiderosis in spleen, bone marrow kidneys; increased, kidney weight at 1%; growth arrest at 0.1% and 1.0%, pronounced anemia at 1%; mild anemia 0.1%; resistance to hypotonicity of erythrocytes; impaired liver function as evidenced by BSP test at 1.0%; no morphological changes seen in kidneys at autopsy, but possible increases in weight of kidneys and spleen; no impaired kidney function.	Thomas et al., 1967b; De Eds, 1963

*Route - oral; vehicle - diet

NR - Not reported

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polycystic kidney disease have been written by Crocker et al. (1971, 1983), Darmady et al. (1970) and Opdyke (1978).

As seen from Table 5-8, long-term dietary administration of diphenylamine to rats results in toxic effects characteristic of polycystic kidney disease at levels ≥0.10% (Thomas et al., 1967a). No adverse effects in rats were observed at ≤0.01%. Several investigators administered diets containing much higher levels (1.0-4.0%) in order to study the time-course of appearance and increasing severity of the lesions (Safouh et al., 1970; Eknoyan et al., 1976; Evan and Gardner, 1976; Gardner et al., 1976; Evan et al., 1978; Philbert et al., 1979; Kime et al., 1962; Woodhouse et al., 1965).

Chronic dietary administration of diphenylamine to mice at 50, 100 or 250 ppm (0.005, 0.01 or 0.025%) for up to 92 weeks resulted in dose-related increases in Heinz body formation in erythrocytes (Coulston et al., 1971). At 250 ppm, increased spleen weight and increased hemosiderosis of the spleen occurred, as well as increased liver weights. No increased incidences of histologic changes in any tissue were observed.

Thomas et al. (1967b) also treated dogs with diphenylamine at dietary levels of 0, 0.01, 0.10 or 1% for 2 years. No histologic changes were observed in kidneys, but fatty changes in the liver, hemosiderosis in spleen, bone marrow and kidneys, impaired liver function as evidenced by the BSP test, growth inhibition and anemia evidenced by reduced erythrocyte counts and hemoglobin concentrations were observed at 1.0%. Erythrocyte counts and hemoglobin concentrations were mildly depressed at 0.10% and may represent the threshold for diphenylamine-induced anemia in dogs. Growth arrest was also observed at 0.1%, but no effects were observed at 0.01%.

Recently, a toxic impurity in diphenylamine was identified by Clegg et al. (1981) which is thought to be the substance that induces polycystic kidney disease. It is N,N,N-triphenyl-p-phenylenediamine, formed when diphenylamine is heated. The studies of Crocker et al. (1972) indicated that the administration of purified diphenylamine or freshly manufactured diphenylamine resulted in a lower incidence of cystic kidney changes in rats (see Section 5.3.). Other toxic impurities in commercial diphenylamine were examined by Safe et al. (1977), who found that o-biphenylamine, o-cyclohexylaniline and p-biphenylamine in the preparations studied and in preliminary testing in pregnant rats induced polycystic kidney disease in the newborn. Results of this testing were similar to those of the studies done by Crocker et al. (1972).

5.6. OTHER RELEVANT INFORMATION

Levenstein (1976) reported an acute dermal LD_{50} in rabbits >5 g/kg and an oral LD_{50} in rats of 1.165 g/kg. Epstein (1976) and Volodchenko (1975) reported an oral LD_{50} in rats of 3.2 g/kg. Oral administration of 1 mmol diphenylamine/kg to a cat caused methemoglobin formation (Alexander et al., 1965). Korolev et al. (1976) reported an acute oral LD_{50} for mice of 1750 mg/kg and 2000 mg/kg for rats. An oral LD_{50} for guinea pigs was reported to be 300 mg/kg (NIOSH, 1976).

Diphenylamine given by gavage daily to rats for 14 days at doses >2 mmol/kg (338 mg/kg) caused necrosis affecting 20% of the papillary apex of the kidney, a reduced capacity to concentrate urine, polyuria, azotemia, a reduced ability to secrete acid urine following an oral ammonium-ion load and grossly elevated absolute kidney weight (Hardy, 1974).

Severe kidney lesions were produced in dehydrated lambs given diphenylamine in an unstated dose for an unstated period of time (Salisbury et al., 1969).

Several other organic chemicals, 5,6,7,8-tetrahydrocarbazole-3-acetic acid, biphenyl, polychlorinated biphenyls, (2,4,5-trichlorophenoxy) acetic acid, and 2-amino-4,5-diphenylthiazole, cause similar polycystic lesions in animals (Crocker et al., 1983). Polycystic kidney disease can be induced in newborn rats, rabbits, hamsters and mice with certain forms of steroids (Crocker et al., 1983). In tests of 32 non-steroidal, anti-inflammatory drugs and analogues of cellular swelling, diphenylamine did not induce swelling and membrane permeability changes at a concentration of 0.6 mM (Famaey and Whitehouse, 1973).

Hong et al. (1974) studied the effects of diphenylamine on sodium and water transport across toad skin and bladder. Diphenylamine induced changes in the sodium transport system across toad skin and interfered with water permeability of the urinary bladder, decreasing ADH-induced passive net water flow. These phenomena could play a role in facilitating renal cyst formation after prolonged administration of diphenylamine to rats.

In a bioassay for antioxidants done by Epstein et al. (1971), diphenylamine gave protection at a concentration of 10 µg/mℓ against photodynamic injury of isolated rat-liver mitochondria from benzo[a]pyrene; at a concentration of 100 µg/mℓ, slight photodynamic effects were seen. Diphenylamine at a concentration of 8 µM has been observed to be a powerful inhibitor of the ferrous ion-mediated degradation reaction of cytochrome P-450 and of lipid peroxidation in bovine adrenal cortex mitochondrial preparations (Wang and Kimura, 1976), suggesting the involvement of a radical species other than $O_2^{\cdot}$ and OH•. It is further suggested that these two processes are closely related. Obviously, the peroxidation reaction of unsaturated fatty acids of membrane phospholipids has important

biological significance, particularly in maintaining microsomal and mitochondrial enzyme activities. The liver and kidney would certainly be affected if these processes were disrupted.

Nizamani (1983) studied the mode of action of diphenylamine pesticides containing N,N-diphenylamines and N-substituted N,N-diphenylamines. Effects on mitochondrial oxidative phosphorylation were studied in mice and insects, or on the photosynthetic reactions of spinach chloroplasts. These compounds acted as uncouplers of mitochondrial oxidative phosphorylation or had inhibitory effects on photosystem II electron transport. In mice, these compounds caused hypothermia, rapid rigor mortis and brain edema.

An inhibition of oxygen consumption of 58% was observed with diphenylamine in a system involving noradrenaline-induced respiration in isolated brown fat cells prepared from adult hamsters (Pettersson et al., 1980).

In an assay using human lung fibroblasts (MRC-5) and radioactively labeled nucleotides to test membrane permeability, diphenylamine applied to a cell monolayer caused 92% release of nucleotide (Thelestam et al., 1980)

Diphenylamine has weak anthelmintic effects when administered orally at 100 mg/kg to infected rats or mice (Selivanova et al., 1972) or at 200 mg/kg in infected mice (Izard-Verchere et al., 1971). Diphenylamine administered orally to either rats or mice at 100 mg/kg showed weak anticholinesterase activity (Selivanova et al., 1972).

Diphenylamine affects cell wall phospholipid content in Enterobacter species (Neu and Winshell, 1972), and converts Escherichia coli from serum resistance to serum sensitivity (Feingold, 1969). Growth in the presence of diphenylamine caused complement-resistant strains of E. coli to become complement-sensitive, affecting amounts of extractable O and K antigens and synthesis of basal core antigens, all of which are lipopolysaccharide in

nature (Howard and Glynn, 1971). Diphenylamine inhibited vitamin K_2 and carotenoid synthesis in Staphylococcus aureus, but had no detectable effect on the formation of the membrane-bound electron transport system (Hammond and White, 1970). Diphenylamine inhibits benzoquinone formation (Kakutani, 1967; Sugimura and Rudney, 1962) and naphthoquinone formation (Salton and Schmitt, 1967). Depending on the concentration and the organism, diphenylamine inhibits (Kakutani, 1967) or does not inhibit steroid synthesis (Olson and Knizley, 1962), and diphenylamine affects (Cho et al., 1964) or does not affect (Olson and Knizley, 1962) fatty acid synthesis.

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

The acute lethality of a 31% emulsifiable concentrate of diphenylamine was determined in rainbow trout, Salmo gairdneri (Schneider, 1979). The 24-, 48- and 96-hour LC_{50} values were 6.60, 5.20 and 3.75 mg/ℓ. Using analytical grade diphenylamine, Tonogai et al. (1982) reported 24- and 48-hour LC_{50} values of 4.0 and 2.2 mg/ℓ for the medaka, Oryzias latipes.

6.2. CHRONIC TOXICITY

Veith et al. (1979) conducted 32-day bioconcentration tests of diphenylamine in fathead minnows, Pimephales promelas, and reported no deaths at an exposure level of 0.0437 mg/ℓ.

6.3. PLANT EFFECTS

Pertinent data regarding the effects of diphenylamine on aquatic plants were not located in the available literature as cited in the Appendix.

6.4. RESIDUE

The BCF of diphenylamine determined in fathead minnows, P. promelas, exposed at 0.0437 mg/ℓ for 32 days was 30 (tissue concentration:water concentration) (Veith et al., 1979).

6.5. OTHER RELEVANT INFORMATION

In the luminescent bacteria, Photobacterium fischeri, the minimum concentration of diphenylamine causing a decrease in bioluminescence was 0.2 mg/ℓ after ~2 minutes of exposure (Bulich, 1979).

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The ACGIH (1980) has adopted a TWA-TLV of 10 mg/m³ and a STEL of 20 mg/m³. Also, the ACGIH (1980) noted that diphenylamine is irritating to mucous membranes in dust or vapor form; a TLV of 10 mg/m³ is recommended for diphenylamine dust.

According to the U.S. EPA (1982), an ADI of 3.6 mg/day was based on a NOAEL of 0.51 mg/kg/day calculated from the TLV for human inhalation exposure. FAO/WHO (1976) estimated an ADI for man to be 0-0.02 mg/kg bw. The estimate was based on no effect levels in dogs, rats and mice; however, the method for calculating the ADI was not explained and was not apparent. The Federal Register (1962) lists tolerances for residues of diphenylamine as follows: 10 ppm in or on apples to cover residues from preharvest spray or use of impregnated wraps; 0 ppm in meat or milk.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of diphenylamine were not located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

Diphenylamine was not oncogenic in a 2-year dietary study in rats when tested at levels ≤1.0% (Thomas et al., 1967a), or after a single gavage dose of 300 mg/rat in female rats observed for 6 months (Griswold et al., 1966). No increased tumor incidence was observed in mice treated at dietary levels ≤250 ppm (≤0.025%) for 92 weeks (Coulston et al., 1971).

Negative results were obtained for reverse mutation in several strains of Salmonella typhimurium and Escherichia coli with and without S-9, for forward mutation in cultured mouse lymphoma cells with and without S-9 and for unscheduled DNA synthesis in cultured rat hepatocytes (see Table 5-5).

Increased incidences and severity of cystic renal lesions were observed in the offspring of female rats treated with aged commercial grade diphenylamine at 20 mg/day by gavage or at 2.5% in the diet during the last 7 days of gestation (Crocker et al., 1972). Similar results were obtained when contaminants of commercial grade diphenylamine at 20 mg/day were administered; however, purified diphenylamine administration at 20 mg/day resulted in greatly reduced incidences and severity of renal lesions.

Clegg et al. (1981) and Safe et al. (1977) also suggested that toxic impurities acquired during manufacture or from heating or aging contribute to the biological effects of diphenylamine.

Dose-related decreased litter sizes were observed in a two-generation feeding study in rats treated at dietary levels of 0.1-0.5% (1000-5000 ppm) (Thomas et al., 1967a); however, the decrease was believed to be secondary to reduced food intake by the parents.

Several studies of chronic dietary administration of diphenylamine have been performed in rats, mice and dogs (see Table 5-8). Thomas et al. (1967a) found that dietary administration to rats at ≥0.1% (1000 ppm)

resulted in increased incidences and severity of kidney lesions (cystic dilatation and chronic nephritis) compared with controls. In addition, an increased incidence of hyperplasia of the bladder of males was observed at 1% (10,000 ppm). Growth was arrested at 0.5 (5000 ppm) and 1% (10,000 ppm) and females treated at 0.1% (1000 ppm) had significantly reduced body weights. Food consumption was decreased at 0.5 (5000 ppm) and 1% (10,000 ppm). No effects were observed at $\leq$0.01% (100 ppm).

In other studies (Safouh et al., 1970; Eknoyan et al., 1976; Evan and Gardner, 1976; Gardner et al., 1976; Evan et al., 1978; Kime et al., 1962; Woodhouse et al., 1965; Philbert et al., 1979), relatively high dietary levels of diphenylamine (1-4%) were administered to rats to study the time-course of appearance and increasing severity of cystic kidney lesions. An abstract of a study by Philbert et al. (1979), in which rats and guinea pigs were treated at dietary levels of 2 or 4% (20,000 or 40,000 ppm) for an unspecified duration, reported increased mortality, liver necrosis and lung congestion, edema and inflammatory lesions in addition to renal lesions.

Mice treated with diphenylamine at dietary levels of 50-250 ppm had dose-related increases in Heinz body formation in red blood cells but no changes in hematologic parameters (Coulston et al., 1971). At 250 ppm, spleen and liver weights were increased, and there was increased hemosiderosis of the spleen. No increased incidence of histologic changes in the kidney or any other tissue were observed.

Thomas et al. (1967b) observed no histologic changes in the kidneys of dogs fed diets containing 0.01-1.0% (100-10,000 ppm) diphenylamine, but fatty changes in the liver, hemosiderosis in the spleen, bone marrow and kidneys, increased kidney weight, arrested growth, pronounced anemia and impaired liver function occurred at 10,000 ppm. At 1000 ppm there was arrested growth and mild anemia. No effects were observed at 100 ppm.

The dietary level of 100 ppm is a NOEL in rats and dogs. The rats ingested the 0.01% diphenylamine diet for 2 years, at which time the males averaged 400 g in weight and had consumed an average of 0.9 g of diphenylamine or 2.25 g/kg (Thomas et al., 1967a). The female dogs fed the 0.01% diphenylamine diet for 2 years averaged 9.09 kg in weight, each having consumed 14 g or 1.54 g/kg of the compound (Thomas et al., 1967b). By dividing the above intakes by 730 days, the NOELs for rats and dogs are respectively equivalent to 3.1 and 2.1 mg/kg/day. In the mouse study, 50 ppm could be considered a NOAEL, but the suitability of this study for deriving an ADI is questionable, since the study by Coulston et al. (1971) is unpublished, was reviewed only briefly by FAO/WHO (1976) and the biological significance of increased Heinz body formation in the absence of hematologic changes is uncertain. The next highest dietary level in the studies in rats and dogs is 1000 ppm, at which rats had renal lesions and dogs had arrested growth and anemia. Based on author's estimate of unaffected food consumption, 1000 ppm is equal to 31 mg/kg/day for rats and 21 mg/kg/day for dogs. Therefore, the LOAEL for chronic dietary exposure to diphenylamine is 21 mg/kg/day, and the most suitable NOEL, below which no adverse effects were observed, is 3.1 mg/kg/day from the rat study. Using an uncertainty factor of 100 (10 for interspecies extrapolation and 10 to protect the most sensitive individuals of the human population), an ADI of 0.031 mg/kg/day or 2.17 mg/day for a 70 kg man is derived.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

Several chronic studies describing the effects of oral exposure to diphenylamine were summarized in Table 5-8. In addition, effects on the offspring of female rats treated during gestation were described in Section 5.3., and a reproduction study was summarized in Section 5.4. Data used to calculate CSs are summarized in Table 9-1.

The reproduction study of Thomas et al. (1967a) is not included in Table 9-1 because the apparent reduction in litter size with increasing dietary concentration was secondary to reduced food intake of the parents. Several chronic feeding studies (Safouh et al., 1970; Eknoyan et al., 1976; Evan and Gardner, 1976; Gardner et al., 1976; Evan et al., 1978; Kime et al., 1962; Woodhouse et al., 1965) are not included in Table 9-1 because the relatively high dietary concentrations (1.5-2.5% or 15,000-25,000 ppm) in these studies were administered to rats to study the time-course of appearance and increasing severity of polycystic kidney disease, an effect also observed at lower concentrations ($\geq$0.10% or 1000 ppm in the diet) (Thomas et al., 1967a). Data from the studies in which diphenylamine was administered in the diet to pregnant rats (Crocker et al., 1972; Crocker and Vernier, 1970) are not included in Table 9-1 because the equivalent doses in mg/kg/day are higher than that used in the portion of the Crocker et al. (1972) study, whereby daily gavage dosing of rats during gestation resulted in polycystic kidney disease in the offspring. Finally, data from the Philbert et al. (1979) study are not included because the rats and guinea pigs were dying within the first 6 months of dietary exposure to 2 or 4% (20,000-40,000 ppm).

For the studies included in Table 9-1, dosages in mg/kg/day were calculated from the dietary levels, assuming that the amount of food consumed/day

TABLE 9-1

Composite Scores for Toxicity of Diphenylamine

Species	Dose/Exposure	Chronic Human MED (mg/day)	RV_d	Effects	RV_e	CS	RQ	Reference
Rat	50 mg/kg/day (1000 ppm in diet for 2 years)	598	1.3	Increased incidence and severity of polycystic renal disease and chronic nephritis	7	9.1	1000	Thomas et al., 1967a
Rat	250 mg/kg/day (5000 ppm in diet for 226 days)	2992	1	Suggestion of red blood cell destruction, not further described	4	4	5000	Thomas et al., 1957
Rat	500 mg/kg/day (10,000 ppm in diet for 2 years)	5985	1	Increased incidence of hyperplasia of bladder, bladder weight not reported	3	3	5000	Thomas et al., 1957
Rat	57 mg/kg/day by gavage, last 7 days of gestation	682	1.2	Polycystic renal disease in offspring, no maternal toxicity	8	9.6	1000	Crocker et al., 1972
Mouse	6.5 mg/kg/day (50 ppm in diet, 92 weeks)	34	3.2	Increased number of Heinz bodies in red blood cells in absence of other hematologic changes	2	6.4	1000	Coulston et al., 1971
Mouse	32.5 mg/kg/day (250 ppm in diet, 92 weeks)	172	2.1	Increased weight of liver, spleen; increased hemosiderosis in spleen; increased number of reticulocytes in blood, but no changes in hematologic parameters	4	8.2	1000	Coulston et al., 1971
Dog	29 mg/kg/day (1000 ppm in diet for 2 years)	1187	1	Arrested growth with normal food consumption, slightly decreased red blood cell count	4	4	5000	Thomas et al., 1967b
Dog	290 mg/kg/day (10,000 ppm in diet for 2 years)	11,871	1	Fatty changes in the liver, increased hemosiderosis in spleen, liver and bone marrow, pronounced reduction in red blood cell count and hemoglobin concentration, increased kidney weight, impaired liver function (BSP test)	7	7	1000	Thomas et al., 1967b

is equivalent to 5% of the body weight of rats, 13% of the body weight of mice and 2.9% of the body weight of dogs. The equivalent chronic human MEDs were calculated by multiplying the animal dosage in mg/kg/day by the cube root of the ratio of the animal weight (0.35 kg for rats, 0.03 kg for mice and 14 kg for dogs) to the human weight (assumed to be 70 kg), and multiplying by 70 kg. The RV_ds associated with the MEDs range from 1-3.2. In animals, the effects observed associated with the MEDs were ranked as follows. Increased incidence and severity of polycystic kidney disease has an RV_e of 7, except when observed in the offspring of rats treated during gestation and, as a fetotoxic effect, receives an RV_e of 8. The suggestion of red cell destruction that was not further described was considered roughly equivalent to an atrophic change, hence, an RV_e of 4. Increased incidence of bladder hyperplasia without evidence of hypertrophy ranks 3. Increased number of Heinz bodies without other hematologic changes observed in mice ranks 2, while increased liver and spleen weights along with hemosiderosis of the spleen is a more serious effect, receiving an RV_e of 4. The growth inhibition in dogs is ranked 4, while the impaired liver function along with other effects has an RV_e of 7.

The CSs for these dose-effect data are obtained by multiplying the RV_d by the RV_e. The highest CS of 9.6 was obtained from the study of Crocker et al. (1972), in which offspring of rats treated by gavage with diphenylamine at 57 mg/kg/day during the last 7 days of gestation had polycystic renal lesions. The CS corresponds to an RQ of 1000 (Table 9-2).

9.2. WEIGHT OF EVIDENCE FOR CARCINOGENICITY AND DERIVATION OF POTENCY FACTOR ($F=1/ED_{10}$)

According to SRC (1983), pertinent data regarding the carcinogenicity of diphenylamine in animals were not located in the available literature; however, several negative studies were summarized in Section 5.1. of this

TABLE 9-2

Diphenylamine

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral
Dose*:	682
Effect:	polycystic kidney disease in offspring
Reference:	Crocker et al., 1972
RV_d:	1.2
RV_e:	8
Composite Score:	9.6
RQ:	1000

*Equivalent human dose

profile (see Tables 5-1, 5-2 and 5-4). In a 2-year feeding study, no increased incidence of tumors was found in rats treated at dietary levels ≤1.0% (10,000 ppm) (Thomas et al., 1967a). Female rats treated by gavage with a single dose of 300 mg/rat did not develop tumors after 6 months of observation (Griswold et al., 1966). Mice maintained on diets containing diphenylamine at ≤250 ppm for 92 weeks did not have increased incidences of tumors compared with controls (Coulston et al., 1971). Data regarding the carcinogenic effect of diphenylamine in humans were not located in the available literature as cited in the Appendix.

Since positive studies of the carcinogenic potential of diphenylamine were not available, the derivation of the potency factor is precluded. This chemical should be placed in IARC Group 3, as it cannot be classified as to its carcinogenicity for humans. Also, according to the U.S. EPA Cancer Assessment Group's proposed cancer risk guidelines, this chemical would be in group D, not adequate evidence for evaluation as a human carcinogen.

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APPENDIX

Literature Searched

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in November, 1984, with the exception of the TOXLINE, which was conducted in March, 1984 and was provided by Dynamac Corp. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. 486 p.

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ITII (International Technology Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

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USITC (U.S. International Trade Commission). 1983. Synthetic Organic Chemicals. U.S. Production and Sales, 1982, USITC Publ. 1422. Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book, Vol. 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish Wildl. Serv. Resource Publ. 137. Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California. State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. PB 269605. Prepared for the U.S. EPA, Washington, DC.

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